

Imaging as a Biomarker: Standards for Change Measurements in Therapy

14-15 September 2006, NIST, Gaithersburg, MD

The Osteoarthritis Initiative (OAI): A Public-Private Partnership

Charles Peterfy, M.D., Ph.D.

Chief Medical Officer

Synarc, Inc.

San Francisco, CA

Osteoarthritis is a Major Unmet Medical Need

- Highly prevalent, chronic, debilitating and costly
 - 8% of the US population (21 M people) have physician-diagnosed OA
 - Many more have undiagnosed or subclinical OA
 - 50% >65 years: frequent knee pain and X-ray OA
 - But, only 1 in 6 consult a physician
 - By 2020, 20% (70 M people) >65 y
 - ⇒ 35 M Americans with X-ray OA
 - >200,000 total knee replacement procedures for OA
- Only symptomatic therapy
- No preventative or disease-modifying therapies (DMOADs) with proven efficacy and safety



Barriers to OA Drug Development

- Inadequate understanding of OA pathophysiology
 - Link between structural abnormalities and clinical outcomes
 - ⇒ Difficulty identifying potentially modifiable therapeutic targets
- Epidemiological studies and clinical trials to elucidate these have to be large, long, difficult and expensive
- Existing cohorts offer valuable info, but are too small and inaccessible
- Lack of biomarkers which are suitably valid, discriminative and feasible



The Osteoarthritis Initiative: A Public-Private Partnership



Academia

NIH funded contracts

Access to public database and specimens



Industry

Study planning
Scientific input
Financial backing
Data & specimens

Government

NIH: Financial input
Contract funding
Holder of public database
Specimen repository

FDA



Goals of OAI

- Produce a public research resource
 - Identify and validate imaging, biochemical and genetic biomarkers for OA
 - Characterize early natural history and progression of OA
 - Evaluate risk and prognostic factors (including biomarkers) for OA onset and progression
- Main focus on knee OA
 - Limited data on hip and hand OA



Approach to Meet OAI Goals

- Prospective cohort study of knee OA
 - Diverse and representative sample of people with knee OA or at risk of developing knee OA
 - Serial measurements (annual)
 - Imaging of knee, hip and hand
 - Biospecimens for biochemical and genetic markers
 - Clinical assessment (joint Sx, disability) and risk factors
 - ⇒ Public data archive on the web
 - ⇒ Archived images for distribution to users
 - ⇒ Archived biospecimens available by application



Infrastructure and Organization

- Government Partners

- National Institute of Arthritis & Musculoskeletal and Skin Diseases (NIAMS)
 - Gayle Lester (Project Officer)
- National Institute on Aging (NIA)
- National Center for Complementary & Alternative Medicine
- National Center on Minority Health & Health Disparities
- National Institute of Biomedical Imaging and Bioengineering
- National Institute of Dental & Craniofacial Research
- Office of Research on Women's Health
- Office of the Director, NIH



Infrastructure and Organization

- Pharmaceutical Partners
 - GlaxoSmithKline
 - Christine Dabrowski and others
 - Merck & Company, Inc.
 - Chan Beals and others
 - Novartis Pharmaceuticals Corporation
 - Monica Luchi, and others
 - Pfizer, Inc
 - Marie Pierre Hellio LeGraverand-Gastineau, and others
 - *Provide funding and participate in scientific decisions*



Infrastructure and Organization

- Clinical Centers

- University of Maryland / Johns Hopkins University
 - Marc Hochberg, Joan Bathon
- Memorial Hospital Rhode Island / Brown University
 - Charles Eaton, Timothy McAlindon
- Ohio State University
 - Rebecca Jackson
- University of Pittsburgh
 - Kent Kwoh
- *Subject recruitment and enrollment*
- *3.0 T Siemens Trio MR scanner installed at each center, dedicated to OAI*



Infrastructure and Organization

- Data Coordinating Center
 - University California San Francisco (Michael Nevitt)
- Imaging QA Center
 - Synarc, Inc. (Charles Peterfy)
- Steering Committee
- Observational Study Monitoring Board (OSMB)
- Consultants and Subcontractors



Imaging Work Group

- F. Boada
- W. Carter
- B. Dardzinski
- F. Eckstein
- J. Evelhoch
- D. Felson
- G. Gold
- B. Goodpaster
- M-P. Hellio Le Graverand
- M. Kothari
- P. Lang
- G. Lester
- M. Nevitt
- C. Peterfy
- T. Pellas
- C. Resnick
- D. Robertson
- E. Schneider
- L. Sharma
- G. Tung
- T. Woodworth



Progression and Incidence Cohorts

Number

1,330

Progression:

Sx knee OA
at baseline



Follow for progression
(Sx, function, structure)

3,215

Incidence:

Risk factors for
Sx knee OA



Follow for incident
Sx knee OA and other
endpoints (X-ray OA)

190 incidents
expected

200

“Nonexposed” control group:
No Sx, no X-ray OA,
No risk factors



Subjects: All Cohorts

- Inclusion
 - Men and Women
 - Ages 45 -79 years
 - All ethnic minorities (19%)
- Exclusion
 - Contraindications to MRI
 - History of inflammatory arthritis
 - RA Sx and medication screen
 - Bilateral end-stage disease (severe JSN and/or bilat TKR)



Examination Schedule



- * 50% Progression cohort get 18 and 30 mo visits (MRI, biospecimens, Sx)



Designing the Imaging Protocol

- Provide imaging data on as many joint structures and features believed to be relevant to OA as possible
- Provide images able to support as broad a range of existing and anticipated measurement methods for each structure and feature as possible
- Balance scientific requirements for image quality and consistency against practical needs of high throughput and patient retention

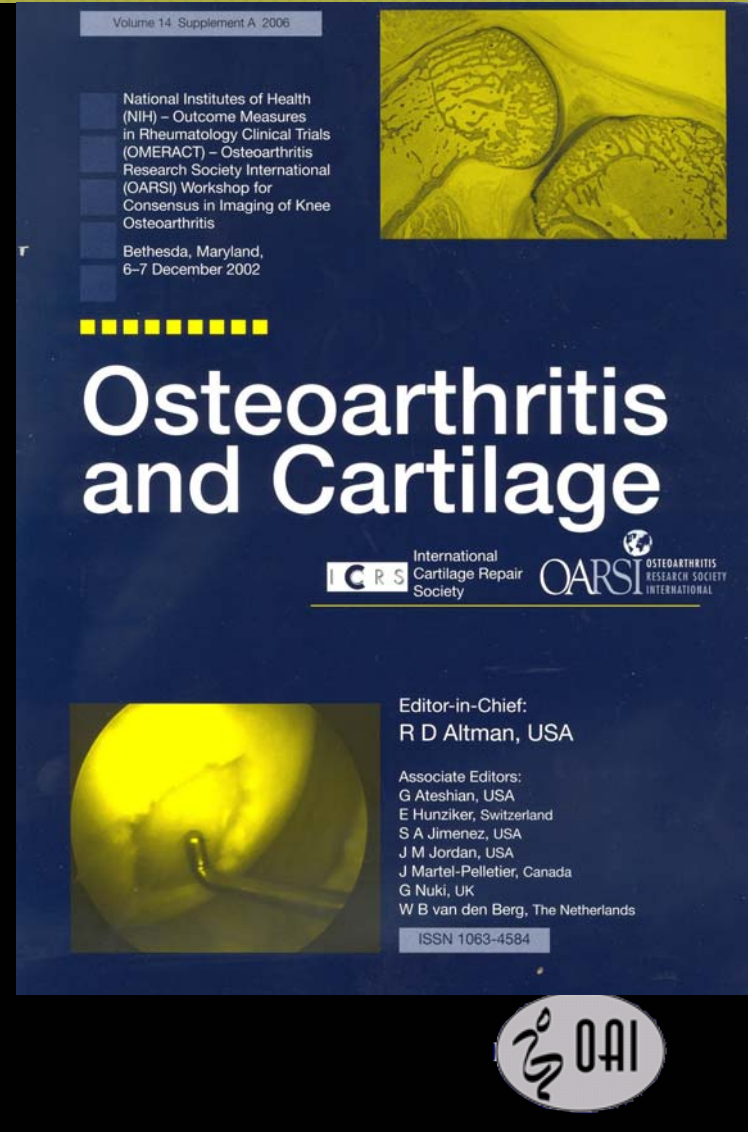


MRI Protocol: Key Considerations

1. Which articular structures and OA features to focus?

- Articular Cartilage
- Osteophytes
- Bone marrow edema
- Menisci
- Synovial effusion
- Cruciate and collateral ligaments
- Subarticular bone cysts
- Periarticular bursa
- Thigh muscles

OMERACT-OARSI Workshop for
Consensus on OA Imaging, Bethesda, Dec
2002



MRI Protocol: Key Considerations

2. What measurement methods (quantitative and semi-quantitative) to support for each?
 - Most established existing biomarkers:
 - Cartilage volume / thickness (regional)
 - Semiquantitative scoring of cartilage and other structures
 - e.g., WORMS
 - Should also support as many future analyses as possible

MRI Protocol: Key Considerations

3. Subject tolerance

- 60 min – 75 *min*

4. Generalizability of the results

- Availability of hardware and pulse sequences
 - Commercial systems and pulse sequences
- Standardized vs. diverse systems and pulse sequences
 - Identical, dedicated, state of the art systems at each site
 - Standardized protocol
 - ⇒ 3T MRI (Siemens Trio): ↑ resolution / speed, avoid obsolescence
 - Extrapolation of 3T data to 1.5T data?
 - Could not borrow protocols established for 1.5T



MRI Protocol: Key Considerations

5. Future utility

- Images must support broadest range of analyses possible *now and tomorrow*

Image Quality Control

- Goals
 - Uniform high-quality artifact-free images from all sites
 - Longitudinal consistency of key parameters
 - SNR, CNR, signal homogeneity, spatial distortion
 - Comparability of images from all 4 sites
 - Minimum need for repeat imaging by preemptive correction of slowly developing problems

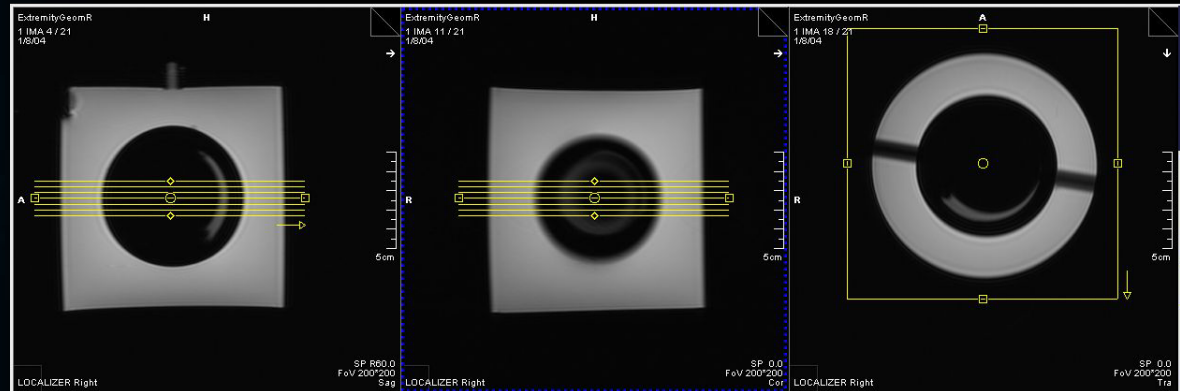


Image Quality Control

- Imaging procedure manuals
- Central and local training of imaging personnel
 - Technologists
 - Local radiologists
- On-going technical feedback
- Site visits to qualify imaging facilities

Image Quality Control

- Acceptance testing
- MRI system performance monitoring
 - Phantoms (ACR and OAI)
 - Regular performance tests
- Image quality
 - Check for protocol adherence
 - Critical image quality criteria
 - Anatomical coverage
 - Artifacts
 - Feedback to sites



Public Data Release


<http://w.w.w.oai.ucsf.edu/datarelease/>

OAI:Home - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Home Search Favorites RSS Print Mail New Tab

Address <http://www.oai.ucsf.edu/datarelease/> Go Links

 **OsteoArthritis Initiative** a knee health study Promoting Health for You & Future Generations

About OAI Data & Documentation Publications My Account Contact Sitemap

>> Home

The Osteoarthritis Initiative

a multi-center, four-year observational study of men and women

The OAI is a nationwide research study, sponsored by the [National Institutes of Health](#) (part of the Department of Health & Human Services), that will help us better understand how to prevent and treat *knee osteoarthritis*, one of the most common causes of disability in adults.

OAIOnline is the name for this website, which provides access to [the Osteoarthritis Initiative](#) (OAI) study documentation and data.

Create an account now!

You must have an account and accept the terms of a Data Use Agreement before you can download or explore clinical data. Please go to [My Account](#) and create a new account now.

New Features

Generate basic statistics online using the *DataExplorer* available in the [Data & Documentation](#) section. (requires an account and acceptance of the terms of a Data Use Agreement)

Data News

1-2-3 Data. [Three quick steps](#) to download the clinical data.


What's Available as of 6/25/2006

Clinical	Baseline questionnaire and exam data for the first half of the cohort (~2600 participants). (download from web)
Imaging	Baseline X-RAY and MRI images for a 200 participant sample (available upon request).

OAIOnline Technical Requirements

OAIOnline is designed to work best with [Internet Explorer 6+](#) or [Netscape Navigator 7+](#), and [Adobe Acrobat Reader 5+](#). Firefox and Safari browsers will also work well. All the browsers mentioned above and Acrobat Reader are freely available.

Important: OAIOnline is intended as a means to learn about and retrieve the data



OAI osteoarthritis initiative
a knee health study

Internet

Public Data Release

<http://w.w.w.oai.ucsf.edu/datarelease/>

- General information about OAI and its design
- Description of study data, procedures and materials
- On-line access to forms, operating manuals and data documentation
- Limited on-line data exploration
- Clinical data sets available for download to registered users
- Images distributed on various electronic media
- Biospecimens available by application to NIAMS-administered Biospecimen Resource Allocation Committee

The screenshot shows a web browser window titled "http://www.oai.ucsf.edu/datarelease/dataexplorer.asp - Micros...". The page content includes a "DataExplorer" header with a "Help" link. A note states: "variable name= 'visit prefix' + 'variable root'". Below this, it explains that statistical measures depend on the data type of each variable, providing examples for categorical (P02SEX, P02RACE, P02KSURG) and continuous (V00AGE, P01HEIGHT, P01KPACTD) variables. A "Subset example" section shows how to filter data based on age, weight, and surgery status. The interface features two main sections: "Statistics for a Single Variable" and "Joint Statistics for Two Variables". Each section has input fields for variable names and optional subsetting criteria, along with "Go" and "Clear" buttons. The browser's status bar at the bottom shows "Done" and "Internet".

http://www.oai.ucsf.edu/datarelease/dataexplorer.asp - Micros...

DataExplorer [Help](#)

Note: variable name= "visit prefix" + "variable root".

Statistical measures returned will depend on the data type of each variable.
Example **categorical** variables are: P02SEX, P02RACE, P02KSURG
Example **continuous** variables are: V00AGE, P01HEIGHT, P01KPACTD

Subset example: if you want data from participants >60 yrs and >85 kg who have had knee surgery, enter the following in the subsetting criteria box:
V00AGE>60 AND P01WEIGHT>85 AND P02KSURG=1

Statistics for a Single Variable

variable name

subsetting criteria (optional)

Joint Statistics for Two Variables

variable1 name variable2 name
 X

subsetting criteria (optional)

Done Internet

Image Analyses

- OAI will make available a limited number of image assessments to address broad questions
 - Relationship between baseline structural and biochemical markers and risk factors with:
 - Onset or progression of X-ray JSW and MRI cartilage markers
 - Onset or progression of symptoms and disability
 - Relationship between changes in structural and biochemical markers with:
 - Onset or progression of X-ray JSW and MRI cartilage markers
 - Onset or progression of symptoms and disability



Image Analyses

- Baseline radiographic assessments that were done by readers at the clinical sites to assign subcohorts
 - Presence of definite tibiofemoral osteophytes (OARSI 1-3)
 - Mild-moderate (OARSI 1-2) vs. severe (OARSI 3) medial tibiofemoral joint-space narrowing

Image Analyses

- Central assessments of Progression subcohort TBD by Steering Committee and contracted out

- Knee X-ray:
JSW and subjective score at BL and FU →



- Knee MRI:
cartilage volume / thickness at BL and FU →
semiquantitative score of OA features at BL



- Hand X-ray:
presence and severity of OA at BL
- Pelvis X-ray:
presence and severity of OA at BL



The Osteoarthritis Initiative

- OAI represents a new research model:
 - Creation of public resources:
 - database, images & specimen repository
- Scientific partnership:
 - Academic and industry scientists
- Novel funding mechanism for research:
 - Involvement of multiple companies and NIH to pool resources
- Other consortia have since been established

